Introduction:

I have been asked to supplement my earlier adverse event analysis with an analysis of Bard's predicted possible failure rates and occurrence ratings as contained in its DFMEAs for various IVC filter products. My opinions are given below, along with Exhibits A, B, and C. My CV is attached as Exhibit D. A listing of testimony given in the last four years is attached as Exhibit E. My hourly litigation consulting rate for preparing reports is $700. All of my statistical opinions were derived using standard statistical techniques.

Per Bard's internal SOPN0700120, a Failure Mode Effects Analysis is a systematic process used to identify potential product related failures. Per this SOP[1], the Design Failure Mode and Effect Analysis (DFMEA) is the FMEA method used to identify and evaluate potential failure modes as they relate to design of the product, subassembly, components, and materials. [redacted]

I have also attached conversion charts allowing for specific comparisons between various changes in Occurrence ratings within the categories of the DFMEAs for each of these filters (See Ex. C.). This allows someone to compare rating changes in any given category from [redacted]

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Rebecca Betensky, Ph.D.

Date

Filter Migration Test Results:

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which is useful for individuals as it is a measure of instantaneous relative risk. For analyses at the population level, the risk ratio (which does not take into account exposure time) is a useful measure under some conditions. The use of sales as the denominator does not adjust for time at risk for the AE of interest. This means that estimates of risk are not comparable among products that have different overall person time at risk, unless the risk of the AE is highest close to its implantation and decreasing after that. However, because the SNF was a permanent filter, while Recovery was retrievable, it is reasonable to assume that adjusting for calendar years of sales, there would be greater person time at risk associated with SNF than with Recovery. This would mean that the RRR's present underestimates of the reporting incidence rate ratios, as they multiply them by the ratio of person time exposure of Recovery divided by SNF. Additionally, the adverse events reported for SNF are likely from some implantations that occurred prior to 2000, which are not reflected in the sales numbers that form the denominators of the reporting risk ratios. This means that the estimates for SNF are biased upward and thus the reporting risk ratios are biased downward.

- <u>Temporal effects in reporting</u> ("Weber effect"): Increased reporting can be observed soon after the launch of a drug, and then decrease over time. This does not appear to be the case in this analysis, in which the RRR's mostly increase over time. Because this analysis includes approximately five years of follow-up after the removal of the Recovery device from the market, this would not be of concern for Recovery. This would be of greater concern for the newest products, such as G2X and Eclipse, which is why I have separately reported results for each product versus SNF. Furthermore, although the SNF was launched in 1990, the first death associated with it occurred in 1997 (BPVE-01-00268632, page 22).

- <u>Reports generated by publicity</u> ("notoriety effect" or "stimulated reporting"): This is known to occur, for example, after FDA warnings appear. It is important to look at timing of the "notoriety effect" to understand what, if any impact, the notoriety has had on reporting. Additionally, if these warnings do not differentially affect the devices, then this does not invalidate the use of the RRR as an estimate of the RR. An FDA warning letter (BPV-17-01-00193337) was sent to Bard on July 13, 2015. It was concerned with manufacturing violations of the Recovery Cone Removal System. It was additionally concerned with violations of Medical Device Reporting requirements, including not reporting to the FDA within 30 days of an event and not submitting complete patient information. While this letter might have generated stimulated reporting, since it was issued in 2015, it would not have any effect on the data used in my analysis. There were no earlier letters regarding concerns about adverse events associated with the Recovery filter, or other Bard products.

- <u>Confounding or "channeling bias"</u>: Confounders are patient specific factors, such as age or gender or hypertension, for example, that are associated both with use of a particular device, such as Recovery, and with the AE, such as migration. If the analysis is conducted without adjustment for confounders, the RRR may be biased for the RR. However, if there are patient specific factors associated with use of a particular device, but not with the AE, or conversely, if there are patient specific factors that are associated with the AE, but not with use of a particular

device, the lack of adjustment for them in the analysis does not produce bias. I am not aware of any individual level data that include potential confounding factors.

Summary

- The Recovery filter is associated with statistically significantly higher risks of the AE's of interest than the SNF filter. This is seen based on data through Q2'03 (November 2007 for tilted filter) and consistently through July 2010. The extremely small p-values convey the strong reliability of these findings. The extremely large magnitudes of the reporting risk ratios suggest that even if there was substantially increased reporting of Recovery relative to SNF (or, equivalently, substantially less underreporting of SNF), the risk ratios for the adverse events could still be considerably larger than 1. Furthermore, if the estimated risk ratios had been considered to be due to an imbalance in the reporting of adverse events, given their large magnitudes, it seems that the company likely would have carefully evaluated this through increased monitoring. This does not appear to have been done.
- The G2 and G2X filters likewise show statistically significantly higher risks of the AE's relative to SNF, over time and AE's, with the exclusion of death due to filter embolization. The RRR's for G2 for tilted filter are not significant until the data are extended through November 2007 and they are not significant for filter fracture until the data are extended through November 2009. The RRR's for G2X are significant for the data are extended through November 2009, except for caval perforation.
- The Eclipse, Meridian, and Denali also show statistically significantly higher risks of fractures relative to SNF over time.
- While there are several issues with the available data sources that must be considered when interpreting the strong and consistent results of this analysis, they, alone, do not offer a plausible interpretation of the results that is consistent with no elevation of risk for Recovery (or other products) versus SNF. I have evaluated several of these through sensitivity analyses, which all produced results consistent with the original data.

In conclusion, the best available adverse event data for the filters considered provide compelling evidence in favor of increased risks of the adverse events that I considered. The reporting risk ratios are generally extremely large, , which in association with their very small p-values, multiple sensitivity analyses, and consistency over time, products and AE's, suggest highly robust increased risks of adverse events for Recovery relative to SNF, and similarly, in most cases, for G2 and G2X, and with respect to fractures for Recovery, G2, G2x, Eclipse, Meridian, and Denali. While these may partially reflect some differential reporting, it is implausible that they would be entirely explained by this.

the AE fully explains the elevated risk ratio, it would require the probability of reporting of Recovery to be 20 times that of SNF. If the company believed that there truly was no elevation in risk associated with Recovery due to SNF, but that all of the signals of elevated reporting risk were due to differential underreporting, it seems likely that they would have increased their monitoring and corrected this problem, especially if underreporting of SNF were due to decreased detection due to its permanence. The fact that this was not done, as evidenced by the *increasing* reporting risk ratios over time and the 2015 FDA warning letter (p. 1, 4, BPV-17-01-00193337), suggests that underreporting does not fully explain the reporting risk ratios.

A concrete instance of underreporting is the lack of SNF filter fracture events for the years 2012-2014. I handled this by using the number of events and number of sales from the cumulative analysis (through November, 20009) with the largest fracture event rate for SNF. I additionally addressed it in sensitivity analysis by further increasing the SNF fracture event rate by adding 5 fractures to the total. However, the true number of events remains unknown for 2012-2014.

In summary, while the reporting risk ratios may involve some degree of underreporting, which makes them imperfect estimates of the actual risk ratios, there is strong evidence across time periods and across AE's of similar degrees of severity to suggest that the true risk ratios are considerably larger than the null value of one.

- Overestimation of denominators: I have used sales data as a proxy for the number of patients who were implanted with the devices. In fact, not every device that was sold was actually implanted in a patient. I addressed this concern by considering in a sensitivity analysis the effect of discounting the sales numbers (through July 2010) by 20%. The reporting risk ratios for this analysis do not change from the original analysis and the p-values are all highly statistically significant ($p<1.0e-7$). If the proportion of filters implanted among those sold does not differ by filter, then this overestimation of exposure does not affect the risk ratio estimation (and would have only negligible effect on the associated p-values). And given that it does not differ by AE prevalence (without differing by filter), this could not explain the observed RRR's given their variance across AE's.

- Counting and data errors: As discussed above, there are discrepancies among company data sheets and even small errors can have large effects on small numbers of events. I addressed this concern by considering in a sensitivity analysis the effect of adding 5 to each of the adverse event totals for SNF in the data through July 2010. The reporting risk ratios are 11.1 (death due to filter embolization), 48.1 (migration), 13.4 (perforation), 48.9 (migration+), 24.5 (filter fracture+). These are all highly statistically significant ($p<1.0e-5$). Based on my analysis of the Bard AE reports, these errors were present for Recovery and not for SNF, and they all underestimated AE counts for Recovery.

- No person-time exposure/cannot calculate incidence rates and ratios: Although sales data by month are available, person-time cannot be reliably calculated because it is unknown when devices are removed or replaced. This would be necessary to calculate the incidence rate ratio,

Denali

As of **December, 2014**, there was a statistically significant increased reporting risk ratio for **filter fracture** (RRR 2.1, p = 0.025) for the **Denali** compared to the SNF.

With respect to the updated fracture analysis, I conducted a sensitivity analysis in which I added 5 events to the number of SNF fractures. With one exception, all of the comparisons that were statistically significant in my original analysis remained so under this analysis, and most remained highly statistically significant. The comparison of Denali versus SNF in 2014 lost its statistical significance, although the RRR point estimate remained elevated at 1.7 (p = 0.114, 95% confidence interval = 0.9-3.3). **Potential Limitations and responses**

There are potential limitations to this analysis that need to be considered when interpreting the results:

- Underreporting: adverse events are generally considered to be underreported to the databases, and potentially differentially by severity of adverse event and by drug or medical device. If only a_1% of occurrences of a particular AE are reported for device 1 and a_2% of occurrences of that AE are reported for device 2, then the RRR will be biased for the true risk ratio, RR, as it will equal $(a_1/a_2)\times$RR. If $a_1=a_2$ then the RRR is unbiased for the RR. If $a_1<a_2$ (i.e., the extent of underreporting for device 1 is greater for device 1 than for device 2), and the true RR is greater than 1, then the RRR is a conservative estimate of the RR (i.e., it is closer to 1 than the RR). It is important to recognize that underreporting in and of itself is not problematic. Rather, differential underreporting of the higher risk device is what leads to bias. And even if there was differential underreporting of the higher risk device, given the variation in reporting relative risks across adverse events, the differential reporting would have had to have been highly variable across adverse events. This does not seem plausible given the severity of the adverse events considered. Given the magnitude of the RRR's, and their variability across adverse events, it seems implausible that differential underreporting by filter could fully explain the deviation of the observed RRR's from 1.

  The estimates of RR provide insight into the magnitude of the underreporting of SNF relative to Recovery that would be necessary to obtain the estimates that were obtained, if the true risk ratio were 1 (i.e., no difference in risk between products). For example, the RRR for Recovery versus SNF for migration events, through July 2010, is 288. This indicates that if there is truly no difference in risk of migration between Recovery and SNF, this reporting risk ratio of 288 could only arise if the probability of reporting a migration event for SNF is 288 times less than the probability of reporting a migration event for Recovery. For example, if 80% of migration events were reported for Recovery, then it would have to be the case that 0.28% of migration events were reported for SNF. Assuming that the company believed that the products were equivalent in their risks of migration, this indicates that they allowed an extremely high level of underreporting for SNF. If there was underreporting of SNF events, but of a more plausible magnitude, such as 50%, then the reporting risk ratio would have been 160 rather than 288. Many of the reporting risk ratios are around 20. Again, this suggests that if underreporting of

= 11, p < 0.0001), and **fracture plus detachment of component** (RRR = 3, p < 0.0001) even after assuming in a sensitivity analysis that there were 5 additional adverse event reports associated with the SNF.

As of **July 31, 2010**, there were statistically significant increased reporting risk ratios for **migration** (RRR =131, p < 0.0001), **caval perforation** (RRR = 18, p < 0.0001), **migration plus embolization** (RRR = 35, p < 0.0001), and **filter fracture plus detachment of component** (RRR = 5, p < 0.0001) for the **G2 and G2x (combined)** compared to the SNF.

As of **December, 2010**, there were statistically significant increased reporting risk ratios for **filter fracture** (RRR 2.5, p =0.006) for the **G2x** compared to the SNF. These RRR's increased through 2011 (4.5), 2012 (5.2), 2013 (6.4), and 2014 (6.8), with p-values < 0.0001.

As of **December, 2010**, there were statistically significant increased reporting risk ratios for **filter fracture** (RRR 6, p < 0.0001) for the **G2 and G2x (combined)** compared to the SNF. These RRR's increased through 2011 (6.9), 2012 (7.5), 2013 (8.6), and 2014 (9.5), with similar p-values.

As of **May, 2011**, there was a statistically significant increased reporting risk ratio for **filter fracture** (RRR 10.1, p < 0.0001) for the **G2x** compared to the SNF.

As of **May, 2011**, there was a statistically significant increased reporting risk ratio for **filter fracture** (RRR 11.8, p < 0.0001) for the **G2 and G2x (combined)** compared to the SNF.

Eclipse

As of **July 31, 2010**, there were statistically significant increased reporting risk ratios for **migration** (RRR = 20, p =0.022), and **caval perforation** (RRR = 5, p 0.017) for the **Eclipse** compared to the SNF. A marginally statistically significant increased reporting risk ratio was maintained for **caval perforation** (RRR = 4, p=0.056) even after assuming that there were 5 additional adverse event reports associated with the SNF.

As of **May, 2011**, there was a statistically significant increased reporting risk ratio for **filter fracture** (RRR 3.6, p = 0.005) for the **Eclipse** compared to the SNF.

As of **December, 2011**, there were statistically significant increased reporting risk ratios for **filter fracture** (RRR 2.9, p =0.0003) for the **Eclipse** compared to the SNF. These RRR's increased through 2012 (4.5), 2013 (5.3), and 2014 (5.8) with similar p-values < 0.0001.

Meridian

As of **December, 2012**, there were statistically significant increased reporting risk ratios for **filter fracture** (RRR 6, p < 0.0001) for the **Meridian** compared to the SNF. These RRR's increased through 2013 (10.6), and 2014 (11.5) with similar p-values < 0.0001.

As of **November 30, 2009**, there were statistically significant increased reporting risk ratios for **migration** (RRR =82, p < 0.0001), **caval perforation** (RRR = 4, p < 0.0001), **tilted filter** (RRR infinite, p =0.0005), **migration plus embolization** (RRR = 20, p < 0.0001), and **filter fracture plus detachment of component** (RRR = 2.65, p < 0.0001) for the **G2** compared to the SNF.

As of **December, 2009**, there was ae statistically significant increased reporting risk ratio for **filter fracture** (RRR 6.5, p < 0.0001) for the **G2** compared to the SNF.

As of **July 31, 2010**, there were statistically significant increased reporting risk ratios for **migration** (RRR =144, p < 0.0001), **caval perforation** (RRR = 19, p < 0.0001), **migration plus embolization** (RRR = 38, p < 0.0001), and **filter fracture plus detachment of component** (RRR = 6, p < 0.0001) with the **G2** compared to the SNF. These substantial and statistically significant increased reporting risk ratios were maintained for **migration** (RRR = 24, p < 0.0001), **caval perforation** (RRR = 12, p < 0.0001), **migration plus filter embolization** (RRR = 16, p < 0.0001), and **fracture plus detachment of component** (RRR = 5, p < 0.0001) even after assuming in a sensitivity analysis that there were 5 additional adverse event reports associated with the SNF.

As of **December, 2010**, there was a statistically significant increased reporting risk ratio for **filter fracture** (RRR 7.1, p < 0.0001) for the **G2** compared to the SNF.

As of **May, 2011**, there was a statistically significant increased reporting risk ratio for **filter fracture** (RRR 12.4, p < 0.0001) for the **G2** compared to the SNF.

As of **December, 2011**, there were statistically significant increased reporting risk ratios for **filter fracture** (RRR 7.7, p < 0.0001) for the **G2** compared to the SNF. These RRR's increased through 2012 (8.2), 2013 (9.5), and 2014 (10.5), with similar p-values.

<u>G2x and G2/G2x combined</u>

As of **November 30, 2009**, there were statistically significant increased reporting risk ratios for **migration** (RRR = 11, p =0.032), **tilted filter** (RRR infinite, p =0.009), and **migration plus embolization** (RRR = 4, p =0.025) for the **G2x** compared to the SNF.

As of **November 30, 2009**, there were statistically significant increased reporting risk ratios for **migration** (RRR =67, p < 0.0001), **caval perforation** (RRR = 3, p =0.0002), **tilted filter** (RRR infinite, p =0.0005), **migration plus embolization** (RRR = 17, p < 0.0001), and **filter fracture plus detachment of component** (RRR = 2.09, p =0.003) for the **G2 and G2x (combined)** compared to the SNF.

As of **July 31, 2010**, there were statistically significant increased reporting risk ratios for **migration** (RRR =94, p < 0.0001), **caval perforation** (RRR = 14, p < 0.0001), **migration plus embolization** (RRR = 26, p < 0.0001), and **filter fracture plus detachment of component** (RRR = 4, p < 0.0001) for the **G2x** compared to the SNF. These statistically significant increased reporting risk ratios were maintained for **migration** (RRR = 15, p < 0.0001), **caval perforation** (RRR = 8, p < 0.00015), **migration plus filter embolization** (RRR

As of **November 30, 2007**, there were statistically significant increased reporting risk ratios for **filter embolization death** (RRR infinite, p < 0.0001), **migration** (RRR = 114, p < 0.0001), **caval perforation** (RRR = 9, p < 0.0001), **filter fracture** (RRR = 81, p < 0.0001), **tilted filter** (RRR infinite, p < 0.0001), **migration plus embolization** (RRR = 85, p < 0.0001), and **filter fracture plus detachment of component** (RRR = 15, p < 0.0001) for the **Recovery** compared to the SNF.

As of **November 30, 2009**, there were statistically significant increased reporting risk ratios for **filter embolization death** (RRR infinite, p < 0.0001), **migration** (RRR = 135, p < 0.0001), **caval perforation** (RRR = 12, p < 0.0001), **tilted filter** (RRR infinite, p =0.0005), **migration plus embolization** (RRR = 52, p < 0.0001), and **filter fracture plus detachment of component** (RRR = 17, p < 0.0001) for the **Recovery** compared to the SNF.

As of **December, 2009**, there were statistically significant increased reporting risk ratios for **filter fracture** (RRR 28.5, p < 0.0001) for the **Recovery** compared to the SNF.

As of **July 31, 2010**, there were statistically significant increased reporting risk ratios for **filter embolization death** (RRR infinite, p < 0.0001), **migration** (RRR = 288, p < 0.0001), **caval perforation** (RRR = 21, p < 0.0001), **migration plus embolization** (RRR = 109, p < 0.0001), and **filter fracture plus detachment of component** (RRR = 30, p < 0.0001) for the **Recovery** compared to the SNF. These statistically significant increased reporting risk ratios were maintained for **filter embolization death** (RRR = 11, p < 0.0001), **migration** (RRR = 48, p < 0.0001), **caval perforation** (RRR = 13, p < 0.0001), **migration plus filter embolization** (RRR = 48, p < 0.0001), and **fracture plus detachment of component** (RRR = 24, p < 0.0001) even after assuming in a sensitivity analysis that there were 5 additional adverse event reports associated with the SNF.

As of **December, 2010**, there were statistically significant increased reporting risk ratios for **filter fracture** (RRR 29.8, p < 0.0001) for the **Recovery** compared to the SNF. These RRR's increased through 2011 (31.5), and 2012 (33.3), with similar p-values.

As of **May, 2011**, there was a statistically significant increased reporting risk ratio for **filter fracture** (RRR 56.2, p < 0.0001) for the **Recovery** compared to the SNF.

<u>G2</u>

As of **February 9, 2006**, there was a statistically significant increased reporting risk ratio for **migration** (RRR = 135, p < 0.0001) for the **G2** compared to the SNF.

As of **June 30, 2006**, there were statistically significant increased reporting risk ratios for **caval perforation** (RRR = 15, p < 0.0001 and **migration** (RRR = 114, p < 0.0001) and a marginally significant increased reporting risk ratio for filter fracture (RRR=5, p=0.0567) for the **G2** compared to the SNF.

As of **November 30, 2007**, there were statistically significant increased reporting risk ratios for **migration** (RRR = 97, p < 0.0001), **caval perforation** (RRR = 5, p < 0.0001), **tilted filter** (RRR infinite, p < 0.0001), and **migration plus embolization** (RRR = 48, p < 0.0001) for the **G2** compared to the SNF.

00188520.XLS for prior to 2003). I was able to infer the migration for SNF through February 9, 2006 using the Bard sheets through Q3 2005 and November 2007 because the SNF counts for migration do not change during this bracketing period. The reporting risk ratio for G2 vs SNF for migration is 135.07, which is highly significantly different from 1 ($p= 2.48e-11$, Fisher's exact test).

G2 vs SNF through June 30, 2006

I have additionally analyzed G2 AE's versus SNF AE's through June 30, 2006. Migration, perforation and filter fracture events for G2 through this date are listed in 2006.06.30.BPVE-01-01035539_.QUADS R002 native G2 caudal migration failure analysis.pdf (slide 7). I used the same source for sales data as for the other analyses that I have conducted (BPV-17-01-00193291.xlsx from 2003 and from BPV-17-01-00188520.XLS for prior to 2003). I was able to infer the migration and perforation counts for SNF through June 30, 2006 using the Bard sheets through Q3 2005 and November 2007 because they do not change during this bracketing period. The filter fractures increase by one during this period, and so to be conservative, I used the November 2007 count for SNF filter fractures. The reporting risk ratio for G2 vs SNF for migration is 114.9, for perforation is 14.9 and for filter fracture is 5.22. The RRR's for migration and for perforation are highly significantly different from 1 ($p<2.2e-16$ and $p=3.6e-11$, respectively).

Analyses of individual filters:

Recovery

As of **June 30, 2003**, there was a statistically significant increased reporting risk ratio for **migration** (RRR = 183, $p <0.0001$) for the **Recovery** compared to the SNF.

As of **February 25, 2004**, there was a statistically significant lower resistance to pressure (as determined through laboratory testing) for the **Recovery** compared to the **SNF** (see statistical analysis below), which was consistent with the increased reporting risk ratio for migration events for the **Recovery** compared to the **SNF**.

As of **April 23, 2004**, there were statistically significant increased reporting risk ratios of **deaths** (RRR infinite, $p =0.0016$), **filter embolization death** (RRR infinite, $p=0.0135$), and **migration** (RRR = 38, $p =0.0001$) for the **Recovery** compared to the SNF.

As of **September 30, 2004**, there were statistically significant increased reporting risk ratios of **filter embolization death** (RRR = infinite, $p < 0.0001$), **migration** (RRR = 24, $p =0.0003$), **caval perforation** (RRR = 4.85, $p =0.006$), **filter fracture** (RRR = 12, $p =0.001$), and **migration plus embolization** (RRR = 33, $p < 0.0001$) for the **Recovery** compared to the SNF.

As of **September 30, 2005**, there were statistically significant increased reporting risk ratios of **filter embolization death** (RRR = infinite, $p < 0.0001$), **migration** (RRR = 63, $p < 0.0001$), **caval perforation** (RRR = 4, $p=0.002$), **filter fracture** (RRR = 53, $p < 0.0001$), **migration plus embolization** (RRR = 54, $p < 0.0001$), and **filter fracture plus detachment of component** (RRR = 6, $p < 0.0001$) for the **Recovery** compared to the SNF.

statistically significant starting in Q3'05 (p=4.3e-12), with decreasing p-values through July 2010 (p<2.2e-16), and the G2 vs SNF comparison is statistically significant starting in November 2009 (p=0.00005).

With respect to the new analysis, I compared the data for the retrievable filters in each time-period with the SNF sales and fracture + detached component reports for November, 2009, because SNF data were not available beyond 2011 and because this time-period contained the highest rate of fractures for SNF, and would amount to a conservative approach as it would use the highest observed rate for fractures for SNF. The reporting risk ratios for filter fractures of retrievable devices compared to SNF are between 2 and 57, using data through 2014. They are between 2 and 34 for earlier comparisons, except for Eclipse in 2010 and Denali in 2013. All of the RRR's that are 2 or greater are statistically significantly different from 1, while those that are less than 2 are not significantly different from 1. There was considerably less data available for Eclipse in 2010 and Denali in 2013, since those were their first years on the market.

Tilted Filter:

The reporting risk ratios are all infinite or undefined due to there being 0 events for SNF. Statistically significant comparisons of Recovery vs SNF and of G2 vs SNF were found using data through November 2007 (p=0.0035 and p=0.000001, respectively) and through November 2009 (p=0.0005 for both comparisons). Comparisons between G2X vs SNF and G2/G2X vs SNF were also significant through November 2009. No new data were reported out to July 2010.

Analyses through specific dates:

In addition to the cumulative analyses described previously, I also considered three specific dates, which are associated with other noted events and issues in which Bard was involved.

Recovery vs SNF through April 23, 2004

The summary table (page 2) of adverse event data through April 23, 2004 (BPVE-01-00268632) does not list filter embolization deaths, filter fracture alone, or migration+filter embolization. The individual listings in subsequent pages of the document reveal some additional information and some errors in the summary table, which I have corrected to include two Recovery deaths due to filter embolization, 5 migration events, and two tilted filters. The reporting risk ratios for Recovery versus SNF for overall fatalities and for filter embolization fatalities are both infinity, the RRR is 38.01 for migration; it is 0 for caval perforation and filter fracture+, and it is infinity for tilted filter. The RRR's for fatalities overall, for filter embolization fatalities, for migration, and for tilted filter are all significantly greater than 1 (p=0.0016, 0.0135, 0.0001, 0.0135, respectively, Fisher's exact test). The other RRR's are not significantly different from 1.

G2 vs SNF through February 9, 2006

I have additionally analyzed G2 AE's versus SNF AE's through February 9, 2006. Migration events for G2 through this date are listed in BPVEFILTER-01-00008355. I used the same source for sales data as for the other analyses that I have conducted (BPV-17-01-00193291.xlsx from 2003 and from BPV-17-01-

Results

The reporting risk ratios and approximate and exact p-values are listed on the summary tab of the Excel workbook.

Analyses of major adverse events:

Filter Embolization Deaths:

By July 2010, there were 15 deaths associated with Recovery filters, and none associated with SNF, G2, G2X or Eclipse filters. A reporting risk ratio cannot be calculated due to the denominator of 0 from SNF, but the exact p-value can be calculated and is 8.3e-11, providing evidence of a highly significant increased risk of reports of death due to filter embolization with Recovery filters as compared to SNF filters. This highly significant result is seen starting from Q3'04 for Recovery vs SNF.

Migration:

The reporting risk ratios for migration for each filter versus SNF are over 20 by July 2010, and are as large as 288. It is striking that the lower 95% confidence bound for the reporting risk ratio for migration for Recovery versus SNF is 40.1. That means that we can be 95% confident that the true reporting risk ratio is at least 40.1. The other lower bounds for the migration risk ratios are 20.2 (G2 vs SNF), 12.9 (G2X vs SNF), 18.5 (G2/G2X vs SNF) and 1.9 (Eclipse vs SNF). In all analyses, the reporting risk ratios are all significantly greater than 1, except for G2 vs SNF (through Q3'05). Similar results are seen when filter embolization is combined with migration ("migration+"), with the exception of the Eclipse vs SNF comparison through July 2010, which has a nominally significant p-value of 0.09. I note that based on the mistaken count of 0 migration events in the original file from the company, the RRR for Recovery versus SNF is 0 and the p-value is 1, indicating that it is not significantly different from 1.

Perforation:

The reporting risk ratios for perforation are between 5 and 22 using data through July 2010 and are roughly 4-12 using the other datasets, except for the comparisons of G2X vs SNF through November 2009, G2 versus SNF through Q3'05 and Recovery versus SNF through Q2'03. These RRR's are 0 due to 0 events in G2X, G2 and Recovery in those periods, but are not significantly different from 1. The Recovery vs SNF comparison is statistically significant starting in Q3'04 ($p=0.0058$), with p-value decreasing to $p<2.2e-16$ through July 2010, and the G2 vs SNF comparison is statistically significant starting in November 2007 ($p=0.00001$), also decreasing to $p<2.2e-16$.

Filter Fracture + detached component(s) :

The reporting risk ratios for filter fracture+ are between 4 and 30 using data through July 2010 (except for the Eclipse vs SNF RRR, which is 0.47). They are between 1.5-17 for earlier comparisons, except for 0's in a few cases, as for perforation. All of the RRR's that are larger than 1 are statistically significant, and those less than 1 are not significantly different from 1. The Recovery vs SNF comparison is

I calculated the p-values using two methods. For the first, I used approximate calculations that rely on large numbers. This approach approximates the natural log of the RRR divided by its approximate standard error as a normally distributed random variable and calculates the p-value on the basis of this approximation. The formula for the approximate standard error of the log(RRR) is given by:

$$\sqrt{\frac{1}{x1}+\frac{1}{x2}-\frac{1}{n1}-\frac{1}{n2}}$$

Where x_1 is the number of AE's for the product of interest (e.g., Recovery), x_2 is the number of AE's for SNF, n_1 is the total units sold for the product of interest and n_2 is the total units sold for SNF. Note that if there are 0 events for Recovery (i.e., x_1=0) or for SNF (i.e., x_2=0), this standard error cannot be calculated. In these instances I listed the p-value as "NA."

The second method calculates the p-value for the test of association between sales and AE's and is an "exact" test, meaning that it does not rely on any large sample approximations. I used Fisher's exact test to calculate these p-values. This approach is useful when there are zero AE's, as in many cases an exact p-value can be calculated, while it cannot for the approximate approach.

95% confidence intervals for the reporting risk ratio

I have calculated 95% confidence intervals for the reporting risk ratios for all of the analyses that include data through July 2010. The associated interpretation is that we can be 95% confident that the intervals contain the "true" reporting risk ratio. The lower bound of the interval is of greatest interest, because its distance from the value 1 is informative about the strength of the evidence in the data against a true reporting risk ratio of 1. The greater it is relative to 1, the smaller the associated p-value.

Adjustment for multiple testing

The chances of false positive findings increase with the number of statistical tests conducted. In the setting of analyses of efficacy, it is critical to account for this through some adjustment for the multiple testing, such as a Bonferroni correction. Control of the false positive rate simultaneously increases the false negative rate. Therefore, for analyses of safety, which are most concerned about controlling the false negative rate, it is more conservative not to adjust for multiple testing. The yellow highlighted cells on the summary tab identify those p-values that are less than 0.05. In sensitivity analyses I maintained an overall false positive rate of 0.05 for each AE through a Bonferroni adjustment for the p-values for each AE calculated at the six time periods that I originally considered. This amounts to using a p-value threshold for statistical significance of 0.05/6=0.0083. Because the analysis of the adverse events through April 23, 2004 was a pre-specified analysis of special interest due to a concurrent hold on the Recovery device, and the analyses through February 9, 2006 and June 30, 2006 were also pre-specified due to concurrent events, I did not include them in the joint analysis of the other six time periods and did not adjust the resulting p-values for multiple testing in sensitivity analysis. I additionally applied a Bonferroni correction for the seven time periods that I considered in my January, 2017 analysis; this amounts to using a p-value threshold of 0.05/7=0.007.

or detached components. I considered both the original categories, as well as these enlarged categories. In later years, filter fracture and detached components are only reported together.

Statistical methods:

Reporting Risk Ratio (RRR) to compare AE's among products:

For a given time period, for each product and adverse event (AE), I calculated the reporting AE risk as the number of AE's divided by the total sales in that time period. I then calculated the reporting risk ratio (RRR) as the ratio of the reporting risk of each product to that of SNF. The reporting risk ratio is an estimate of the measure of interest, which is the risk ratio (RR). I discuss below (under Potential Limitations) conditions under which the RRR provides an unbiased or conservative estimate of the RR. Letting x_1 denote the number of AE's for the product of interest, x_2 denote the number of AE's for SNF, n_1 denote the total units sold for the product of interest and n_2 denote the total units sold for SNF, the RRR is defined as

$$RRR=(x_1/n_1)/(x_2/n_2).$$

A value of the RRR that is larger than one reflects a higher risk for the AE for the product of interest than for SNF. An RRR that is less than one reflects a lower risk of the AE for the product of interest than for SNF. Note that if there are 0 events for SNF (i.e., $x_2=0$), the RRR will involve division by 0. I have listed these instances of the RRR as "∞" in my tables. If there are 0 events for Recovery and 0 events for SNF, the RRR involves 0's in both the numerator and the denominator. I have listed these instances of the RRR as "0/0" in my tables. For example, considering data through Q3'05, there were 79,349 SNF units sold and 33,592 Recovery units sold. There were 7 perforations observed among subjects with SNF filters and 13 perforations observed among subjects with Recovery filters. Thus, the RRR for Recovery versus SNF for this time period and for perforations is (13/33,592)/(7/79,349)=4.4. This suggests a 4.4 higher risk for perforation associated with Recovery than with SNF.

I note that the reporting risk ratio is different from the proportional reporting ratio (PRR) and the reporting odds ratio (ROR), both of which use total numbers who were implanted with the devices who report AE's as denominators and not total numbers who were implanted with the devices.

p-values for inference about RRR

To test whether an observed RRR is statistically significantly different from one (i.e., the "null" value), I calculated the p-value. The p-value is the probability that the observed RRR (e.g., 4.4) or an even more extreme RRR (e.g., a larger value than 4.4 or a smaller value than 1/4.4) could have arisen if the true RRR is actually one. If the p-value is very small (e.g., less than 0.05), we either have to believe that a highly unlikely event occurred, or that our presumption that the true RRR is equal to one is incorrect. Since the second possibility is more likely, we accept that explanation, and reject the null hypothesis that the true RRR is equal to one. That is, we conclude that the observed RRR of 4.4 is indeed significantly different from 1.

for G2, but the 14 instances of "tilted filter" were not counted. In the sheet that reports adverse events through July 2010 (BPVEFILTER-01-00050487 - Marauder Report by Manufacturer Summary IVC Filters 10-14-10 v5), 15 deaths due to filter embolization are listed for Recovery, and 0 for SNF, G2, G2X, Eclipse. In contrast, in the sheet that reports adverse events through November, 2009 (BPVE-01-01501003), 16 deaths due to filter embolization are listed for Recovery and 1 is listed for G2.

I have found substantial discrepancies between the company reports that I used for my analysis and internal company reports on Recovery adverse events. For example, in the data report that I used for my report through April 23, 2004 (BPVE-01-00268632), the summary table (page 2) lists 4 migration events, while the individual data list 5 migration events (page 10), the summary table does not list any filter embolization deaths, while the individual data list two deaths associated with migration, which I take to be filter embolization deaths, and the summary table lists one tilted filter, while two are listed in the data reports (page 10). In the data reports that I used through September, 2004 (BPVE-01-00052935-maude), there are 6 migration events and 6 filter fracture events reported for the Recovery device. In a Bard memo dated September 7, 2004 (BPVE-01-01059656), there are 17 migrations and 22 filter fractures reported for Recovery. In the data reports that I used for my report through September, 2005 (BPVE-01-01054793), there are 27 migration events and 45 filter fracture events reported for the Recovery device. In a Bard report titled "Recovery Filter Adverse Events (Migrations/Fractures) (BPVE-01-00436350)," there are 55 migrations and 76 filter fractures reported. These examples indicate that the data reports that I used provided considerably lower numbers of events for Recovery than originally detected by Bard.

The data used for the updated analysis also contain inconsistencies that are relatively minor and unlikely to affect the results. For example, while the data sheets refer to "fractures", the numbers provided appear to correspond more closely to the numbers in the earlier spreadsheets that combined "fractures" and "detachment of component" events. The "G2 Filter – Fracture Analysis" from December 2009 indicates that there were 82 fractures reported for G2 (BPV-17-01-00170706, p. 5), while the "Filter-Fracture Analysis" for November, 2011 indicates that in 2009 there were 79 G2/G2x complaints (BPV-17-01-00170503, p. 5). Where a discrepancy was noted, I used the fracture analysis with the later date, under the assumption that data errors may have been found and corrected over time.

The spreadsheet Bard produced with data cumulative through May, 2011 appears to have a different definition of "fracture" for SNF because it reports 8 SNF fractures (BPVEFILTER-01-00037664), while data from earlier time-periods report more SNF fractures + detached components (e.g., 22 through November, 2009 (BPVE-01-01501003)). The numbers of fractures for the other products are close to those reported in November, 2009 and July, 2010.

Adverse events:

I considered five adverse events: deaths due to filter embolization, filter fracture, migration, perforation and tilt. In some instances of the extracted data in the existing spreadsheets the AE of migration is expanded to include filter embolization and the AE of filter fracture is expanded to include detachment

Introduction:

In this analysis, I compared proportions of adverse event reports of the Recovery, G2, G2x, G2 and G2x combined, and Eclipse vena cava filters relative to their sales, to the proportions of adverse event reports for the SNF VCF. I considered six time periods, which correspond to existing BARD AE reports: 2000- Q2'03, 2000-Q3'04, 2000-Q3'05, 2000-11/2007, 2000-11/2009, 2000-7/2010. In separate analyses, I considered data from 2000-April 23, 2004, which was of special interest due to hold on the Recovery filter that was imposed in the first quarter of 2004, from 2000-February 9, 2006 and from 2000-June 30, 2006.

The above analysis (and discussion below) is identical to my August, 28, 2016 report. Since that time I have conducted an additional analysis based on additional sales and adverse event data, and including the Denali and Meridian devices. I considered fracture reports for an additional six time periods: 2000-2009, 2000-2010, 2000-2011, 2000-2012, 2000-2013, and 2000-2014. In a separate analysis, I considered data from 2000-May, 2011, because Bard did an internal comparison using this time-period.

Data sources:

Data for this analysis are comprised of adverse event reports and monthly sales totals. The adverse event reports were extracted from the MAUDE database that is maintained by the FDA for the purpose of reporting for medical devices, as well as Trackwise (Q2'03: BPVE-01-00196343-maude2000.xls, April 23, 2004: BPVE-01-00268632, Q3'04: BPVE-01-00052935-maude.xls, Q3'05: BPVE-01-01054793.xlsx and BPV-17-01-0193291.xls, 11/2007: BPV-17-01-00188520.xls, 11/2009: BPVE-01-01501003.xls, 7/2010: BPVEFILTER-01-00050487.XLSX for BARD events and BPVEFILTER-01-00174270_2009 AERs.xls, BPVE-01-01706342_January 10 AEs.XLS, BPVEFILTER-01-00043057_July 10 2010.XLS, BPVE-01-00749928_February 10 AEs.XLS, BPVEFILTER-01-00043446_May 10 AEs.XLS, BPVEFILTER-01-00043059_March 10 AEs.XLS, BPVEFILTER-01-00043053_April 10 AEs.XLS, BPVEFILTER-01-00043058_June 10 AEs.XLS for SNF events). The sales data were provided by BARD (BPV-17-01-00193291.xlsx for sales from 2003 and BPV-17-01-00188520.XLS for sales prior to 2003).

For the updated analysis, I used the same sources of sales data, with the exception of the analysis through May, 2011, which contained both sales and adverse event data in BPVEFILTER-01-00037664. The adverse event reports were found in the following documents: 2008: BPV-17-01-00170706, 2009: BPV-17-01-00170503, 2010, 2011 and 2011: BPV-17-01-00170625, 2013: BPV-17-01-00226338, 2014: BPVEFILTER-01-00303182.

Data inconsistencies and errors:

I note that there was an error in the calculation of migration AE's on the Recovery tab of BPV-17-01-00188520.xls: the formula in B2 should be =countif(f7:f444,b1), but actually was hard-coded as "$0.00". This changes the total Recovery migration events from 0 to 37 (cell g18 on the Rates tab, through November 2007). I also note that on the SNF tab of that same sheet, there are two migration events, rather than the one listed on the rate tab, though in a subsequent sheet that event is labeled as filter embolization. In another sheet (BPVE-01-01501003), the 11 instances of "filter tilt" were counted

one filter to another. Examples of this type of comparison are contained below. Additionally, my review demonstrated several observations across the broad categories of migrations, penetrations, perforations and fracture. These are also described below.

Facts/Data Considered:

In performing this analysis, I reviewed the following documents: DFMEA070010, Rev. 0; DFMEA070022, Rev. 1; DFMEA070044, Rev. 3; DFMEA070063, Rev. 2; DFMEA070077, Rev. 1; DFMEA070081, Rev. 4; DFMEA070084, Rev. 0; DFMEA070042. Revs. 0-1; SOPN070012, Rev. 0; SOPN0700120, Revs. 1-14; Document entitled "Filter Launch Dates," found at BPVEFILTER-19-00000058; 30(b)(6) Deposition of Chad Modra, January 26, 2017; Exhibit 762A to said Deposition of Chad Modra; Change Request found at BPVEFILTER-01-00207602; DFMEA070022, Rev. 4; Deposition of Mark Wilson, January 31, 2017; Exhibit 798 to said Deposition of Mark Wilson; and Document entitled "DFMEARates," found at BPVE-01-01035626.

Opinions

Recovery Filter

1. Bard predicted at the January 31, 2003 launch of the Recovery filter that the possible failure rates[3] for penetrations and perforations of the caval wall in the Recovery filter were greater than the possible failure rates for penetrations and perforations of the caval wall in the SNF in all the categories contained in Exhibit A and Exhibit B.
2. As one example, Bard predicted the Recovery filter, at launch, would migrate due to "Inadequate radial force (e.g. Nitinol properties)" resulting in Patient death[4] 1 to 75 times more frequently[5] than it predicted the SNF would migrate as a result of "Inadequate radial strength (e.g. Nitinol properties)" resulting in a "Critical health hazard (e.g. filter embolization to heart or lungs, life threatening." Compare Migration Category 2.1.8 in the Recovery DFMEA and Migration Category 2.1.7 in the SNF DFMEA.
3. As a second example, Bard predicted the Recovery filter, at launch, would penetrate the caval wall due to "Excessive radial force (e.g. Nitinol properties)" resulting in "User/Patient annoyance (major)" 10 to 750 times more frequently than it predicted the SNF would penetrate the caval wall due to "Excessive radial force (e.g. Nitinol

[3] Per SOPN0700120 Bard expresses a possible failure rate in terms of a defined range and each occurrence rating has an assigned range.

[4] In describing the Potential Effects of each Failure Mode in this analysis, I used the "End Effects," as defined in SOPN0700120.

[5] Where these comparisons are expressed as a comparative range, the lower bound was calculated by dividing the minimum probability of occurrence corresponding to the occurrence rating for the comparator device by the maximum probability of occurrence corresponding to the occurrence rating of the SNF. The upper bound of this comparative range was calculated by dividing the maximum probability of occurrence corresponding to the occurrence rating for the comparator device by the maximum probability of occurrence corresponding to the occurrence rating for the SNF. (See Ex. C, Tables (1a), (1b), (2a), and (2b).)

properties)" resulting in a Moderate health hazard.[6] Compare Penetration category 2.2.3 in the Recovery and to Perforation category 2.2.3 in the SNF DFMEA.

G2 Filter

1. Bard predicted at the September 7, 2005 launch of the G2 filter that the possible failure rates for migrations in the G2 filter were greater than or equal to the possible failure rates for migrations in the SNF in all the categories contained in Exhibit A and Exhibit B.
2. Bard predicted at the September 7, 2005 launch of the G2 filter that the possible failure rates for penetrations and perforations of the caval wall in the G2 filter were greater than the possible failure rates for penetrations and perforations of the caval wall in the SNF in all the categories contained in Exhibit A and Exhibit B.
3. As one example, Bard predicted that the G2 filter, at launch, would migrate due to "Inadequate radial strength (e.g. Nitinol properties)" resulting in a potentially "Life Threatening" effect 1 to 75 times more frequently than it predicted the SNF would migrate as a result of "Inadequate radial strength (e.g. Nitinol properties)" resulting in a "Critical health hazard (e.g. filter embolization to heart or lungs, life threatening." Compare Migration Category 2.4.8 in the G2 DFMEA and Migration Category 2.1.7 in the SNF DFMEA.
4. As a second example, Bard predicted that the G2 filter, at launch, would penetrate the caval wall due to "Excessive radial force (e.g. Nitinol properties)" resulting in "Patient Injury" 10 to 750 times more frequently than it predicted the SNF would penetrate the caval wall due to "Excessive radial force (e.g. Nitinol properties)" resulting in a Moderate health hazard. Compare Penetration category 2.5.3 in the G2 DFMEA to Perforation category 2.2.3 in the SNF DFMEA.

G2X Filter

1. At the December 10, 2008 launch of the G2X filter[7], Bard predicted that the possible failure rates for migrations in the G2X filter were greater than or equal to the

[6] Note that, for comparisons contained in this analysis to predicated probabilities of occurrence of the SNF penetrating the caval wall, the label of the Potential Failure Mode utilized is "Perforation of caval wall (Type I)." The description of this Potential Failure Mode within the SNF DFMEA is a "Pinhole created in caval wall." This is the description applied to the Potential Failure Mode "Penetration of caval wall" in the DFMEAs of other Bard IVC filters. (See Ex. B.) This is as opposed to the description of the SNF Potential Failure Mode "Perforation of caval wall (Type II)", which reads "Hole created in caval wall." This is the description applied to the Potential Failure Mode "Perforation of the caval wall" in the DFMEAs of other Bard IVC filters. (See Ex. B.) Therefore, for purposes of this analysis, Perforation of caval wall (Type I) under the SNF DFMEA is referred to herein as penetration of the caval wall.

[7] There are two G2X launch DFMEAs. The Occurrence Ratings in each of these DFMEAs are the same and therefore these statements apply to both.

possible failure rates for migrations in the SNF in all the categories contained in Exhibit A and Exhibit B.[8]

2. At the December 10, 2008 launch of the G2X filter, Bard predicted that the possible failure rates for penetrations and perforations of the caval wall in the G2X filter were greater than or equal to the possible failure rates for penetrations and perforations of the caval wall in the SNF in all the categories contained in Exhibit A and Exhibit B.
3. As one example, at launch, Bard predicted that the G2X filter would penetrate the caval wall due to "Excessive radial force (e.g. Nitinol properties)" resulting in a Moderate health hazard 10 to 150 times more frequently than it predicted the SNF would penetrate the caval wall due to "Excessive radial force (e.g. Nitinol properties)" resulting in a Moderate health hazard. Compare Penetration category 2.9.3 in the G2X DFMEA to Perforation category 2.2.3 in the SNF DFMEA.
4. As a second example, Bard predicted the G2X filter, at launch, would fracture due to "Material fatigue due to movement against osteophyte of a vertebra an IVC side-branch vessel, or some other anatomical anomaly" resulting in Major dissatisfaction 1 to 4 times more frequently than it predicted the SNF would fracture due to "Material fatigue due to movement" resulting in Major dissatisfaction. Compare Fracture category 3.4.2 in the G2X DFMEA to Fracture category 3.2.2 in the SNF DFMEA.

Eclipse Filter

1. At the January 14, 2010 launch of the Eclipse filter, Bard predicted that the possible failure rates for migrations in the Eclipse filter were greater than or equal to the possible failure rates for migrations in the SNF in all the categories contained in Exhibit A and Exhibit B.
2. At launch, Bard predicted that the possible failure rates for penetrations and perforations of the caval wall in the Eclipse filter were greater than or equal to the possible failure rates for penetrations and perforations of the caval wall in the SNF in all the categories contained in Exhibit A and Exhibit B.
3. As one example, at launch, Bard predicted the Eclipse filter would penetrate the caval wall due to "Excessive radial force (e.g. Nitinol properties)" resulting in a Moderate health hazard 10 to 150 times more frequently than it predicted the SNF would penetrate the caval wall due to "Excessive radial force (e.g. Nitinol properties)" resulting in a Moderate health hazard. Compare Penetration category 2.9.3 in the Eclipse DFMEA to Perforation category 2.2.3 in the SNF DFMEA.
4. As a second example, at launch, Bard predicted the Eclipse filter would fracture due to "Material fatigue due to movement against osteophyte of a vertebra an IVC side-branch vessel, or some other anatomical anomaly" resulting in Major dissatisfaction

[8] Bard's sales brochure states the G2X filter combines the best design features of Bard's existing vena cava filters, and this includes the SNF. See deposition of Mr. Wilson at 101:9-102:9; Ex. 798 to Wilson Deposition. The brochure also states that G2X filter has increased migration resistance and enhanced fracture resistance. (Ex. 798 to Wilson Deposition.) Bard did not differentiate subcategories of migrations or fractures in its sales brochure.

1 to 4 times more frequently than it predicted the SNF would fracture due to "Material fatigue due to movement" resulting in Major dissatisfaction. Compare Fracture category 3.1.2 in the Eclipse DFMEA to Fracture category 3.1.2 in the SNF DFMEA.

Meridian Filter

1. At the August 26, 2011 launch of the Meridian filter, Bard predicted that the possible failure rates for migrations in the Meridian filter were greater than or equal to the possible failure rates for migrations in the SNF in all the categories contained in Exhibit A and Exhibit B.
2. At launch, Bard predicted that the possible failure rates for penetrations and perforations of the caval wall in the Meridian filter were greater than or equal to the possible failure rates for penetrations and perforations of the caval wall in the SNF in all the categories contained in Exhibit A and Exhibit B.
3. As one example, at launch, Bard predicted the Meridian filter would migrate in a cephalad direction due to "Appendage fracture (e.g., arm, leg)" resulting in a Critical health hazard 1 to 15 times more frequently than it predicted the SNF would migrate as a result of "Wire fracture/detachment" resulting in a Critical health hazard. Compare Migration category 2.4.4 in the Meridian DFMEA and Migration category 2.1.5 in the SNF DFMEA.
4. As a second example, at launch, Bard predicted the Meridian filter would migrate in a caudal direction due to "Appendage fracture (e.g., arm, leg)" resulting in a Critical health hazard 1 to 15 times more frequently than it predicted the SNF would migrate as a result of "Wire fracture/detachment" resulting in a Critical health hazard. Compare Migration category 2.8.4 in the Meridian DFMEA and Migration category 2.1.5 in the SNF DFMEA.
5. As a third example, at launch, Bard predicted the Meridian filter would perforate the caval wall due to "Excessive radial force (e.g. Nitinol properties)" resulting in a Critical health hazard 1 to 15 times more frequently than it predicted the SNF would perforate the caval wall due to "Excessive radial force (e.g. Nitinol properties)" resulting in a Critical health hazard. Compare Perforation category 2.14.3 in the Meridian DFMEA to Perforation category 2.3.3 in the SNF DFMEA.
6. As a fourth example, at launch, Bard predicted the Meridian filter would fracture due to "Material fatigue due to movement against osteophyte of a vertebra an IVC side-branch vessel, or some other anatomical anomaly" resulting in Major dissatisfaction 2 to 10 times more frequently than it predicted the SNF would fracture due to "Material fatigue due to movement" resulting in Major dissatisfaction. Compare Fracture category 3.1.2 in the Meridian DFMEA to Fracture category 3.1.2 in the SNF DFMEA.

Denali Filter

1. At the May 17, 2013 launch of the Denali filter, Bard predicted that the possible failure rates for migrations in the Denali filter were greater than or equal to the possible failure rates for migrations in the SNF in all the categories contained in Exhibit A and Exhibit B.
2. At launch, Bard predicted that the possible failure rates for penetrations and perforations of the caval wall in the Denali filter were greater than or equal to the possible failure rates for penetrations and perforations of the caval wall in the SNF in all the categories contained in Exhibit A and Exhibit B.
3. As one example, at launch, Bard predicted the Denali filter would migrate in a cephalad direction due to "Appendage fracture (e.g., arm, leg)" resulting in a Critical health hazard 1 to 15 times more frequently than it predicted the SNF would migrate as a result of "Wire fracture/detachment" resulting in a Critical health hazard. Compare Migration category 2.4.4 in the Denali DFMEA and Migration category 2.1.5 in the SNF DFMEA.
4. As a second example, at launch, Bard predicted the Denali filter would migrate in a caudal direction due to "Appendage fracture (e.g., arm, leg)" resulting in a Critical health hazard 1 to 15 times more frequently than it predicted the SNF would migrate as a result of "Wire fracture/detachment" resulting in a Critical health hazard. Compare Perforation category 2.8.4 in the Denali DFMEA to Perforation category 2.1.5 in the SNF DFMEA.
5. As a third example, at launch, Bard predicted the Denali filter would perforate the caval wall due to "Excessive radial force (e.g. Nitinol properties)" resulting in a Critical health hazard 1 to 15 times more frequently than it predicted the SNF would perforate the caval wall due to "Excessive radial force (e.g. Nitinol properties)" resulting in a Critical health hazard. Compare Perforation category 2.14.3 in the Denali DFMEA to Perforation category 2.3.3 in the SNF DFMEA.
6. As a fourth example, at launch, Bard predicted the Denali filter would fracture due to "Material fatigue due to movement against osteophyte of a vertebra an IVC side-branch vessel, or some other anatomical anomaly" resulting in Major dissatisfaction 2 to 10 times more frequently than it predicted the SNF would fracture due to "Material fatigue due to movement" resulting in Major dissatisfaction. Compare Fracture category 3.1.2 in the Denali DFMEA to Fracture category 3.1.2 in the SNF DFMEA.

Conclusions:

1. At the launch of every filter from the G2 forward Bard predicted that the possible failure rates for migrations were greater than or equal to the possible failure rates for migrations in the SNF in all the categories contained in Exhibit A and Exhibit B.
2. At the launch of every filter from the Recovery forward Bard predicted that the possible failure rates for penetrations and perforations of the caval wall were greater than or equal to the possible failure rates for penetrations and perforations of the caval wall in the SNF in all the categories contained in Exhibit A and Exhibit B.

3. In many instances, some of which are described above, Bard predicted substantial increases in failure rates from the Recovery forward, when compared to the SNF. In some cases, the predicted failure rate for a new device could be up to 750 times higher than the rate predicted for SNF. As can be seen from my analysis of adverse event reports, the Recovery, G2, G2x, Eclipse, Meridian, and Denali devices in fact had statistically significant higher rates of adverse event reports than the SNF in various categories and time-periods.

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March 3, 2017

Rebecca Betensky, Ph.D. | Date